Request for permission for oral testimony at Idaho Medicaid's P&T Committee meeting on 04-15-2011

Submission # 7

The following request has been:

- ○ Approved
- ☒ Denied

## Gennrich, Jane - Medicaid

**From:** Paul J Setlak [paul.setlak@abbott.com]
**Sent:** Monday, March 14, 2011 5:41 PM
**To:** Gennrich, Jane - Medicaid; Eide, Tamara J. - Medicaid
**Subject:** Idaho Medicaid P&T Committee Request - Trilipix
**Attachments:** Jones, et al 2010.pdf; Kipnes, et al 2010.pdf

March 14, 2011

Pharmacy & Therapeutics Committee
Attention: Tami Eide, Pharm.D.
3232 Elder Street
Boise, Idaho 83705

Dear Dr. Eide:

Thank you for your unsolicited request for updated clinical information on Trilipix®. Please find enclosed updated clinical information for the product being reviewed, per your direction found on the website (http://healthandwelfare.idaho.gov/Medical/PrescriptionDrugs/PTCommittee/tabid/207/Default.aspx), for consideration as part of the upcoming State of Idaho P&T Committee Drug Review Meeting to be held April 15, 2011.

**Trilipix®**

1. Jones PH, Cusi K, Davidson MH, Kelly MT, Setze CM, Thakker K, et al. Efficacy and safety of fenofibric acid co-administered with low- or moderate-dose statin in patients with mixed dyslipidemia and type 2 diabetes mellitus: results of a pooled subgroup analysis from three randomized, controlled, double-blind trials. *Am J Cardiovasc Drugs.* 2010;10(2):73-84.
2. Year two assessment of fenofibric acid and moderate-dose statin combination: a phase 3, open-label, extension study. Kipnes MS, Roth EM, Rhyne JM, Setze CM, Lele A, Kelly MT, Sleep DJ, Stolzenbach JC. *Clin Drug Investig.* 2010;30(1):51-61.

For full prescribing information, please see the most up to date package insert located at:
Trilipix®: http://rxabbott.com/pdf/trilipix_pi.pdf
Additionally, based on the State of daho promulgated rules regarding "(3) new studies released since the last review," please permit this correspondence to also serve as a request to provide oral presentation based on the clinical updates provided.

Please understand that this information is intended to provide only a clinical update of Trilipix®. If you would like additional information or have more questions please contact me at 773-320-7057.

Thank you and have a wonderful day.

Sincerely,
Dr. Paul Setlak

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Strategy

ORIGINAL RESEARCH ARTICLE

Am J Cardiovasc Drugs 2010; 10 (2): 73-84
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# Efficacy and Safety of Fenofibric Acid Co-Administered with Low- or Moderate-Dose Statin in Patients with Mixed Dyslipidemia and Type 2 Diabetes Mellitus

## Results of a Pooled Subgroup Analysis from Three Randomized, Controlled, Double-Blind Trials

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## Abstract

**Background:** Monotherapy with lipid-modifying medication is frequently insufficient to normalize lipid abnormalities in patients with mixed dyslipidemia and type 2 diabetes mellitus.
**Objective:** To evaluate the efficacy and safety of fenofibric acid + statin combination therapy in this population.
**Study Design:** A pooled, subgroup analysis of three randomized, controlled, double-blind, 12-week trials.
**Setting:** Multiple clinical research facilities in the US and Canada.
**Patients:** Patients with mixed dyslipidemia and type 2 diabetes (n = 586).
**Intervention:** Fenofibric acid (Trilipix®) 135 mg monotherapy; low-, moderate-, or high-dose statin monotherapy (rosuvastatin [Crestor®] 10, 20, or 40 mg; simvastatin [Zocor®] 20, 40, or 80 mg; or atorvastatin [Lipitor®] 20, 40, or 80 mg); or fenofibric acid + low- or moderate-dose statin.
**Main Outcome Measure:** Mean percentage changes in lipid parameters, percentages of patients achieving optimal serum lipid/apolipoprotein levels, and incidence of adverse events.
**Results:** Fenofibric acid + low-dose statin resulted in significantly ($p < 0.001$) greater mean percentage changes in high-density lipoprotein cholesterol (HDL-C) [16.8%] and triglycerides (–43.9%) than low-dose statin monotherapy (4.7% and –18.1%, respectively) and significantly ($p < 0.001$) greater reductions in low-density lipoprotein cholesterol (LDL-C) [–34.0%] than fenofibric acid monotherapy (–5.3%). Similarly, fenofibric acid + moderate-dose statin resulted in significantly ($p \leq 0.011$) greater mean percentage changes in HDL-C (16.3%) and triglycerides (–43.4%) than moderate-dose statin monotherapy (8.7% and –24.2%, respectively) and significantly ($p < 0.001$) greater reductions in LDL-C (–32.6%) than fenofibric acid monotherapy (–5.3%). Compared with low- or moderate-dose statin, fenofibric acid + low- or moderate-dose statin resulted in over 5-fold higher percentages of patients achieving optimal levels of LDL-C, non-HDL-C, apolipoprotein B, HDL-C, and triglycerides simultaneously. Incidence of adverse events was generally similar among treatments.
**Conclusion:** Fenofibric acid + statin combination therapy in patients with mixed dyslipidemia and type 2 diabetes was well tolerated and resulted in more comprehensive improvement in the lipid/apolipoprotein profile than either monotherapy.

[Clinical trials are registered at www.clinicaltrials.gov: NCT00300482, NCT00300456, and NCT00300469].

## Background

Patients with type 2 diabetes mellitus and no clinically evident coronary heart disease (CHD) are considered to have a near-term risk equivalent to those patients without diabetes who have established CHD.[1] Furthermore, CHD patients with diabetes have very high recurrent event rates as well as low CHD event survival rates.[1] As part of a comprehensive program to control risk factors in patients with type 2 diabetes, the American Diabetes Association (ADA) recommends a serum low-density lipoprotein cholesterol (LDL-C) treatment goal <100 mg/dL (<2.59 mmol/L) or <70 mg/dL (<1.81 mmol/L) for highest risk patients, and the recent ADA/American College of Cardiology (ACC) consensus statement additionally recommends goals for serum non-high-density lipoprotein cholesterol (non-HDL-C) <130 mg/dL (<3.37 mmol/L) and apolipoprotein B (ApoB) <90 mg/dL (non-HDL-C <100 mg/dL [<2.59 mmol/L] and ApoB <80 mg/dL for highest risk patients).[2,3]

Many patients with type 2 diabetes have mixed dyslipidemia characterized by high serum triglycerides (TG) and low HDL-C levels in addition to non-optimal serum LDL-C levels.[1] High TG and low HDL-C levels are each independently associated with increased CHD risk,[4,5] and the combination of high TG and/or low HDL-C in addition to suboptimal LDL-C poses a significantly higher risk for cardiovascular events compared with elevated LDL-C alone.[6] A subanalysis of patients with type 2 diabetes and metabolic syndrome in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial further demonstrated that high TG and low HDL-C at baseline were associated with the highest risk of cardiovascular disease (CVD) [17.8% over 5 years], compared with other metabolic syndrome features.[7]

Statin monotherapy is recommended for patients with type 2 diabetes to achieve their LDL-C goal, but often this does not normalize all lipid levels when mixed dyslipidemia is present. Recent retrospective analyses demonstrate that the majority of patients with mixed dyslipidemia on statin monotherapy have nonoptimal serum levels of LDL-C, HDL-C, and TG.[8-10] Considerable risk of cardiovascular events exists in patients receiving statins when abnormal on-treatment serum levels of non-HDL-C, ApoB, TG, and HDL-C remain. For such patients, the ADA and the ADA/ACC consensus statements suggest combining statins with another lipid-altering medication such as niacin or a fibric acid derivative (fibrate).

A potential deterrent to combination lipid drug treatment for patients with type 2 diabetes may be the limited clinical trial data supporting efficacy and safety, compared with statin monotherapy. Recently, the US FDA approved the use of the choline salt formulation of fenofibric acid, a peroxisome proliferator-activated receptor (PPAR)-α agonist, in combination with statins in high-risk patients with mixed dyslipidemia, such as those with type 2 diabetes. This prespecified subgroup analysis of data pooled from three large, double-blind, phase III, randomized, controlled trials[11-13] evaluated the efficacy and safety of fenofibric acid combined with statins in patients with mixed dyslipidemia and type 2 diabetes.

## Subjects and Methods

### Patients

Patients were eligible to enroll if they had mixed dyslipidemia {HDL-C <40 mg/dL (<1.04 mmol/L) [men] or <50 mg/dL (<1.30 mmol/L) [women], TG ≥150 mg/dL (≥1.70 mmol/L), and LDL-C ≥130 mg/dL (≥3.37 mmol/L)} after a 6-week washout of lipid-altering medications. Patients with type 1 diabetes or uncontrolled type 2 diabetes (hemoglobin $A_{1c}$ >8.5%) were excluded (details regarding inclusion/exclusion criteria, calculation of sample sizes, and trial designs have been described previously[14]). This analysis included only patients diagnosed with type 2 diabetes. The diagnosis of type 2 diabetes was based on the discretion of the principal investigator, who utilized the patient's medical history and/or fasting blood glucose measurements performed at the screening visit to make this determination.

### Trial Design

Patients were enrolled in one of three phase III, randomized, double-blind, active-controlled, prospective, multicenter trials of similar design that evaluated fenofibric acid (Trilipix®, Abbott, North Chicago, IL, USA) in combination with low or moderate doses of different statins (rosuvastatin [Crestor®, AstraZeneca, Wilmington, DE, USA],[12] simvastatin [Zocor®, Merck, Whitehouse Station, NJ, USA],[13] or atorvastatin [Lipitor®, Pfizer, New York, NY, USA][11]). Each trial lasted 22 weeks, including a 6-week diet run-in/lipid-altering drug washout period, a 12-week treatment period, and a 30-day safety follow-up period. Trials were conducted in the US and Canada. Fasting blood samples were collected. Trial protocols and associated documents were approved by institutional review boards and/or independent ethics committees. Informed consent was obtained from all patients.

In each trial, randomization was stratified by diabetic status and screening TG level (≤250 or >250 mg/dL [2.83 mmol/L]) prior to assignment in a 2:2:2:2:2:1 ratio to one of six

treatment arms: fenofibric acid 135 mg/day; low-dose statin (rosuvastatin 10 mg/day, simvastatin 20 mg/day, or atorvastatin 20 mg/day); fenofibric acid 135 mg/day + low-dose statin; moderate-dose statin (rosuvastatin 20 mg/day, simvastatin 40 mg/day, or atorvastatin 40 mg/day); fenofibric acid 135 mg/day + moderate-dose statin; or high-dose statin (rosuvastatin 40 mg/day, simvastatin 80 mg/day, or atorvastatin 80 mg/day). The high-dose statin monotherapy group included half the number of patients in the other treatment arms and was intended to act as a clinically relevant reference for safety results. No efficacy comparisons with the high-dose statin group were prespecified and no statistical comparisons with the high-dose statin monotherapy group were performed in this analysis. Data from the three trials were pooled. Planned enrollment of the fenofibric acid + rosuvastatin trial was approximately twice that of the other trials.

### Statistical Analysis

All statistical comparisons were performed separately for each dose of combination therapy. Efficacy endpoints were mean percentage change from baseline to final visit in HDL-C, TG, LDL-C, non-HDL-C, ApoB, ApoAI, very low-density lipoprotein cholesterol (VLDL-C), and total cholesterol; and median percentage change in high-sensitivity C-reactive protein (hsCRP). For HDL-C, TG, and LDL-C, fenofibric acid + low- or moderate-dose statin groups were compared with the fenofibric acid monotherapy group as well as the low- or moderate-dose statin monotherapy group, respectively. For all other efficacy variables, fenofibric acid + low- or moderate-dose statin groups were compared with the low- or moderate-dose statin monotherapy group, respectively. The subgroup of patients with baseline LDL-C >160 mg/dL (>4.14 mmol/L) were also analyzed.

Mean percentage changes were compared using contrast statements within an analysis of covariance (ANCOVA) with the corresponding baseline lipid value as a covariate and with effects for treatment group and screening TG level (≤250, >250 mg/dL). Percentage changes in hsCRP were compared using a non-parametric test (Van Elteren's test using screening TG level as the stratification factor [≤250, >250 mg/dL]). These analyses included patients with both a baseline and at least one post-baseline value (using last observation carried forward). The percentage of patients achieving optimal levels for LDL-C (<100 mg/dL, <70 mg/dL), non-HDL-C (<130 mg/dL, <100 mg/dL), ApoB (<90 mg/dL, <80 mg/dL), HDL-C (>40 mg/dL for men, >50 mg/dL for women), or TG (<150 mg/dL) at the final visit was calculated for each treatment group; each combination therapy dose group was compared with the corresponding dose of statin monotherapy using a Fisher's exact test.

Adverse events were assessed and recorded at each visit, coded using the Medical Dictionary for Regulatory Activities, and summarized. Mean changes from baseline to the final value in fasting blood glucose levels were compared between each combination therapy group and the corresponding monotherapy groups using one-way ANOVA. Adverse events and laboratory measurements occurring through 30 days after the last dose of trial drug were included in the analyses. However, if a patient enrolled in the subsequent 52-week, open-label, extension trial,[15] laboratory measurements and adverse events occurring after the first dose of the trial drug in the extension trial were excluded from analyses.

## Results

### Patient Disposition and Baseline Characteristics

Of the 2698 patients with mixed dyslipidemia who were treated in the phase III trials, 586 (21.7%) had type 2 diabetes, including 53 patients who received high-dose statin monotherapy. 285 patients were treated in the fenofibric acid + rosuvastatin trial, 149 patients were treated in the fenofibric acid + simvastatin trial, and 152 patients were treated in the fenofibric acid + atorvastatin trial. Baseline characteristics for treated patients included in this analysis are presented in table I. Concomitant use of at least one antidiabetic medication was reported for 79.0% of patients. The most common antidiabetic medications used were metformin (51.7%), rosiglitazone (16.2%), glipizide (13.3%), and pioglitazone (11.3%); percentages were comparable among treatment groups. Use of 2, 3, 4, and 5 concomitant antidiabetic medications was reported by 28.3%, 14.2%, 1.2%, and 0.2%, respectively.

### Lipid Efficacy

The combination of fenofibric acid with low-dose statin resulted in substantial improvements to multiple lipid variables, with significantly greater mean percentage changes in HDL-C, TG, non-HDL-C, ApoAI, VLDL-C, and total cholesterol, compared with low-dose statin monotherapy (figure 1 and table II). Reductions in LDL-C, ApoB, and hsCRP were similar comparing fenofibric acid + low-dose statin with low-dose statin monotherapy ($p > 0.05$ for each). Significantly greater mean percentage changes in HDL-C, TG, and VLDL-C were observed with fenofibric acid + moderate-dose statin compared with moderate-dose statin monotherapy (figure 2 and table III). LDL-C reductions were smaller with fenofibric

**Table I.** Baseline characteristics[a]

| Characteristic | Fenofibric acid (n = 105) | Low-dose statin (n = 105) | Fenofibric acid + low-dose statin (n = 106) | Moderate-dose statin (n = 107) | Fenofibric acid + moderate-dose statin (n = 110) |
|---|---|---|---|---|---|
| Gender [n (%)] | | | | | |
| women | 54 (51.4) | 56 (53.3) | 61 (57.5) | 52 (48.6) | 62 (56.4) |
| men | 51 (48.6) | 49 (46.7) | 45 (42.5) | 55 (51.4) | 48 (43.6) |
| Race [n (%)]) | | | | | |
| White | 99 (94.3) | 93 (88.6) | 95 (89.6) | 94 (87.9) | 92 (83.6) |
| Black | 5 (4.8) | 8 (7.6) | 7 (6.6) | 9 (8.4) | 12 (10.9) |
| other | 1 (1.0) | 4 (3.8) | 4 (3.8) | 4 (3.7) | 6 (5.5) |
| Ethnicity [n (%)] | | | | | |
| Hispanic | 10 (9.5) | 9 (8.6) | 14 (13.2) | 14 (13.1) | 15 (13.6) |
| Age (y) [mean ± SD] | 58.3 ± 11.03 | 58.6 ± 9.65 | 60.2 ± 9.20 | 58.0 ± 10.29 | 58.0 ± 9.98 |
| Waist circumference (cm) [mean ± SD] | | | | | |
| women | n = 53<br>104.3 ± 14.11 | n = 54<br>108.1 ± 13.18 | n = 61<br>107.0 ± 16.24 | n = 52<br>107.3 ± 12.43 | n = 60<br>110.8 ± 13.85 |
| men | n = 51<br>114.3 ± 21.17 | n = 49<br>111.4 ± 13.85 | n = 45<br>112.2 ± 18.37 | n = 55<br>109.1 ± 14.17 | n = 48<br>110.5 ± 15.96 |
| BMI (kg/m$^2$) [mean ± SD] | n = 100<br>34.7 ± 7.68 | n = 102<br>34.8 ± 6.38 | n = 98<br>34.3 ± 6.96 | n = 103<br>34.5 ± 6.50 | n = 106<br>35.0 ± 7.23 |
| Nicotine use [n (%)] | | | | | |
| user | 19 (18.1) | 15 (14.3) | 20 (18.9) | 22 (20.6) | 20 (18.2) |
| ex-user | 33 (31.4) | 38 (36.2) | 36 (34.0) | 36 (33.6) | 35 (31.8) |
| non-user | 53 (50.5) | 52 (49.5) | 50 (47.2) | 49 (45.8) | 55 (50.0) |
| Co-morbidities [n (%)] | | | | | |
| CHD[b] | 15 (14.3) | 10 (9.5) | 14 (13.2) | 13 (12.1) | 10 (9.1) |
| hypertension[b] | 83 (79.0) | 81 (77.1) | 83 (78.3) | 81 (75.7) | 83 (75.5) |
| metabolic syndrome[c] | 89 (84.8) | 95 (90.5) | 96 (90.6) | 98 (91.6) | 98 (89.1) |
| Blood glucose (mean ± SD) | | | | | |
| mg/dL | 130.3 ± 42.80 | 133.3 ± 43.56 | 132.2 ± 38.88 | 123.7 ± 24.73 | 128.2 ± 33.75 |
| mmol/L | 7.23 ± 2.38 | 7.40 ± 2.42 | 7.34 ± 2.16 | 6.87 ± 1.37 | 7.12 ± 1.87 |
| $HbA_{1c}$ (%) [mean ± SD] | n = 102<br>6.8 ± 0.81 | n = 104<br>6.8 ± 0.78 | n = 106<br>6.7 ± 0.69 | n = 106<br>6.7 ± 0.63 | n = 109<br>6.7 ± 0.82 |

a The table presents data from all treatment groups except the high-dose statin group, which was not included in any comparisons in this analysis.

b Reported medical history.

c According to National Cholesterol Education Program (NCEP) Adult Treatment Panel III[1] criteria.

**BMI** = body mass index; **CHD** = coronary heart disease; **$HbA_{1c}$** = glycosylated hemoglobin; **SD** = standard deviation.

acid + moderate-dose statin compared with moderate-dose statin monotherapy (–32.6% vs –41.5%, $p < 0.001$); however, reductions in non-HDL-C and ApoB were similar, as were the effects on ApoAI, hsCRP, and total cholesterol ($p > 0.05$ for each).

The percentage of patients simultaneously meeting optimal lipid/apolipoprotein levels that were based on published guidelines[1-3] was determined (figure 3). The percentage of patients simultaneously achieving high-risk category targets (LDL-C <100 mg/dL, non-HDL-C <130 mg/dL, and ApoB <90 mg/dL) was similar with fenofibric acid + low- or moderate-dose statin, compared with low- or moderate-dose statin monotherapy, respectively ($p > 0.05$ for each). However, the percentage of patients simultaneously achieving LDL-C <100 mg/dL, non-HDL-C <130 mg/dL, ApoB <90 mg/dL, HDL-C >40 mg/dL (men) or >50 mg/dL (women),

and TG <150 mg/dL was more than 5-fold higher ($p < 0.001$) with the combination of fenofibric acid + low-dose statin compared with low-dose statin monotherapy, and approximately 7-fold higher ($p < 0.001$) with the combination of fenofibric acid + moderate-dose statin compared with moderate-dose statin monotherapy. The percentages of patients simultaneously achieving the highest-risk category targets of LDL-C, non-HDL-C, and ApoB (<70, <100, and <80 mg/dL, respectively) were substantially lower than those achieving the high-risk category targets, but were comparable between the fenofibric acid + low-dose statin and low-dose statin monotherapy groups (9.3% vs 8.1%, $p > 0.05$) and between the fenofibric acid + moderate-dose statin and moderate-dose statin monotherapy groups (10.4% vs 13.1%, $p > 0.05$).

In the subgroup with higher baseline LDL-C (>160 mg/dL), mean percentage change ± standard error in LDL-C was −45.5 ± 2.82% with fenofibric acid + low-dose statin and −43.5 ± 2.35% with fenofibric acid + moderate-dose statin, both of which were greater than that seen in the overall group. These reductions were similar to those observed with low- and moderate-dose statin monotherapy (−38.5 ± 2.64% and −47.1 ± 2.46%, respectively; $p > 0.05$ for both).

### Safety

The incidence of treatment-emergent adverse events and elevations in laboratory values related to muscle, hepatic, and renal function were evaluated, as well as mean changes in

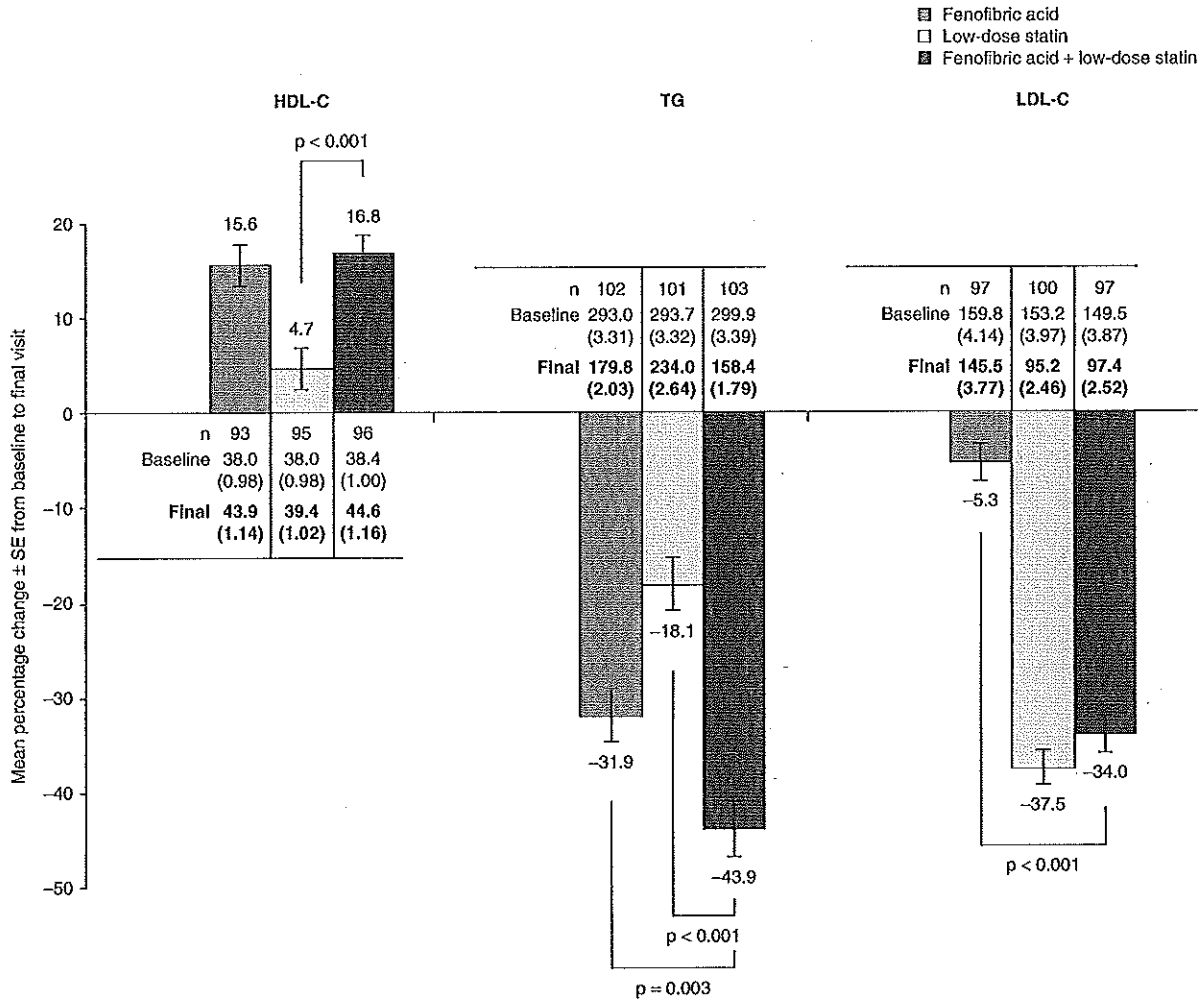


**Fig. 1.** Low-dose treatment group effects on key abnormal lipids in mixed dyslipidemia. Effects of 12-week treatment with fenofibric acid 135 mg monotherapy, low-dose statin monotherapy, or fenofibric acid + low-dose statin combination therapy on mean percentage changes in high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C). Mean values at baseline and final visit are also presented as mg/dL (mmol/L). p-Values are shown for statistically significant differences, comparing combination therapy with fenofibric acid monotherapy or low-dose statin monotherapy. One patient with extreme outlying percentage change values was excluded from the HDL-C and TG analyses. **SE** = standard error.

Table II. Additional efficacy variables[a] – low-dose groups

| Efficacy variable | Fenofibric acid | Low-dose statin | Fenofibric acid + low-dose statin | p-Value[b] |
|---|---|---|---|---|
| **Non-HDL-C** | **n = 93** | **n = 96** | **n = 96** | |
| baseline mean | 223.0 (5.77) | 217.6 (5.63) | 217.2 (5.63) | |
| final mean | 180.1 (4.66) | 139.4 (3.61) | 125.5 (3.25) | |
| % change (mean ± SE) | −17.9 ± 1.75 | −35.9 ± 1.72 | −41.8 ± 1.73 | 0.015 |
| **ApoB** | **n = 101** | **n = 99** | **n = 103** | |
| baseline mean | 147.3 | 144.8 | 144.7 | |
| final mean | 122.4 | 97.2 | 91.3 | |
| % change (mean ± SE) | −15.6 ± 1.53 | −32.7 ± 1.55 | −36.2 ± 1.52 | 0.10 |
| **ApoAI** | **n = 94** | **n = 87** | **n = 93** | |
| baseline mean | 141.3 | 141.2 | 140.9 | |
| final mean | 152.0 | 143.5 | 153.3 | |
| % change (mean ± SE) | 8.1 ± 1.81 | 3.0 ± 1.88 | 10.3 ± 1.82 | 0.006 |
| **hsCRP** | **n = 101** | **n = 99** | **n = 103** | |
| baseline median | 3.05 | 3.27 | 3.66 | |
| % change (median; Q1, Q3) | −12.1; −39.7, 28.4 | −25.5; −52.8, 11.2 | −25.0; −44.2, 19.1 | 0.63 |
| **VLDL-C** | **n = 99** | **n = 95** | **n = 98** | |
| baseline mean | 65.9 (1.71) | 68.6 (1.78) | 66.5 (1.72) | |
| final mean | 36.2 (0.94) | 43.8 (1.13) | 28.7 (0.74) | |
| % change (mean ± SE) | −37.2 ± 3.47 | −31.2 ± 3.54 | −49.7 ± 3.49 | <0.001 |
| **Total-C** | **n = 102** | **n = 102** | **n = 103** | |
| baseline mean | 260.0 (6.76) | 257.3 (6.69) | 255.6 (6.65) | |
| final mean | 224.7 (5.84) | 181.7 (4.72) | 169.8 (4.42) | |
| % change (mean ± SE) | −12.6 ± 1.34 | −29.3 ± 1.34 | −33.2 ± 1.34 | 0.039 |

a Means are presented in mg/dL (mmol/L); hsCRP medians are presented in mg/L.

b Fenofibric acid + low-dose statin compared with low-dose statin monotherapy.

**ApoAI** = apolipoprotein AI; **ApoB** = apolipoprotein B; **hsCRP** = high-sensitivity C-reactive protein; **non-HDL-C** = non-high-density lipoprotein cholesterol; **Q1** = first quartile; **Q3** = third quartile; **SE** = standard error; **total-C** = total cholesterol; **VLDL-C** = very low-density lipoprotein cholesterol.

fasting blood glucose (table IV). In general, clinically meaningful elevations in alanine aminotransferase, creatine kinase, and creatinine were rare. Mean changes in blood glucose levels with fenofibric acid + low- or moderate-dose statin combination therapy were significantly smaller ($p = 0.038$ and $p = 0.040$, respectively) compared with the mean increases in blood glucose observed with the corresponding dose of statin monotherapy.

## Discussion

The practical evaluation of fenofibric acid in combination with commonly administered statins, the large number of patients with mixed dyslipidemia and type 2 diabetes in this subgroup analysis, and the novel assessment of this combination therapy on the percentage of patients meeting optimal lipid levels together provide relevant clinical data to make informed decisions about this type of combination therapy. Fenofibric acid + statin resulted in substantial, simultaneous improvement in multiple lipid/apolipoprotein levels. The lipid efficacy was consistent with the integrated analysis of the overall population of patients with mixed dyslipidemia,[16] and was similar across all three trials, consistent with the expected efficacy associated with each statin.[11-13]

The co-administration of low-dose statin with fenofibric acid resulted in similar LDL-C-lowering efficacy as low-dose statin monotherapy, with substantially greater improvements in HDL-C and TG. In contrast, moderate-dose statin monotherapy, compared with low-dose statin monotherapy, resulted in a numerically larger LDL-C decrease, but small differences

in the mean percentage changes of TG and HDL-C. As our patients treated with low- or moderate-dose statin persisted with high mean TG (234.0 mg/dL [2.64 mmol/L] or 206.6 mg/dL [2.33 mmol/L], respectively) and low mean HDL-C levels (39.4 mg/dL [1.02 mmol/L] or 40.9 mg/dL [1.06 mmol/L], respectively), these data suggest that the addition of fenofibric acid is likely to exert a greater benefit on TG and HDL-C levels than doubling the statin dose in patients with controlled LDL-C levels.

National guidelines and consensus groups recommend lipid treatment targets and/or optimal levels. The ADA classifies patients with type 2 diabetes and known CVD as 'highest risk' and recommends LDL-C <70 mg/dL,[3] while the most recent ADA/ACC consensus classifies patients with type 2 diabetes and at least one additional CVD risk factor as 'highest risk' and recommends LDL-C <70 mg/dL, non-HDL-C <100 mg/dL, and ApoB <80 mg/dL.[2] The percentage of all our patients simultaneously reaching these treatment goals for both high- and highest-risk categories was comparable between combination therapy and corresponding-dose statin monotherapy. Importantly, the co-administration of fenofibric acid and statin was statistically better than statin monotherapy in achieving these three high-risk category goals together with the optimal HDL-C and TG levels (figure 3).

Similar to the results observed in the overall population,[16] as well as previous reports with other fibrate and statin combination clinical trials,[17-19] smaller mean percentage decreases in LDL-C levels were observed with combination therapy

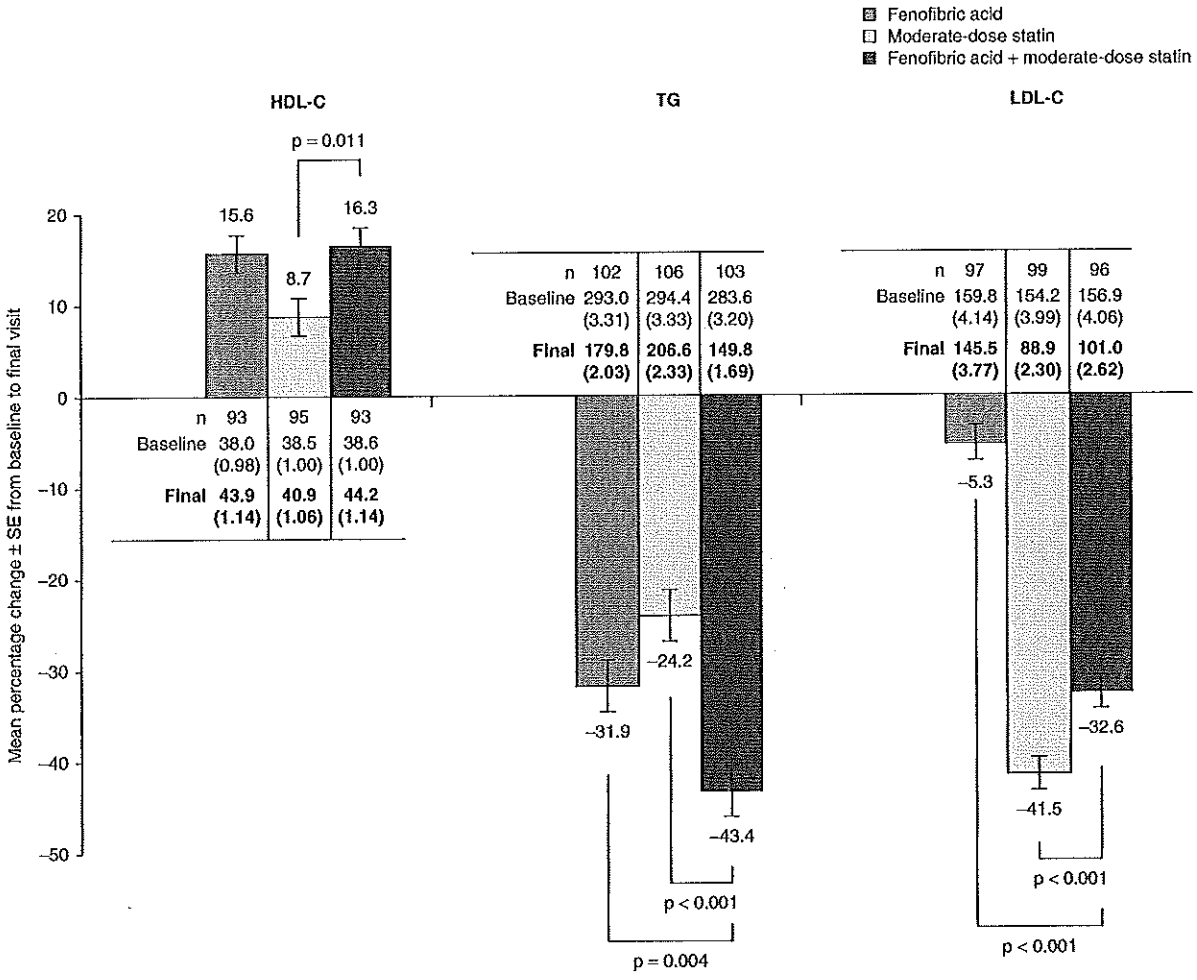


**Fig. 2.** Moderate-dose treatment group effects on key abnormal lipids in mixed dyslipidemia. Effects of 12-week treatment with fenofibric acid 135 mg monotherapy, moderate-dose statin monotherapy, or fenofibric acid + moderate-dose statin combination therapy on mean percentage changes in high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C). Mean values at baseline and final visit are also presented as mg/dL (mmol/L). p-Values are shown for statistically significant differences, comparing combination therapy with fenofibric acid monotherapy or moderate-dose statin monotherapy. **SE** = standard error.

Table III. Additional efficacy variables[a] – moderate-dose groups

| Efficacy variable | Fenofibric acid | Moderate-dose statin | Fenofibric acid + moderate-dose statin | p-Value[b] |
|---|---|---|---|---|
| **Non-HDL-C** | **n = 93** | **n = 95** | **n = 93** | |
| baseline mean | 223.0 (5.77) | 221.2 (5.73) | 218.6 (5.66) | |
| final mean | 180.1 (4.66) | 126.3 (3.27) | 127.7 (3.31) | |
| % change (mean ± SE) | −17.9 ± 1.75 | −42.5 ± 1.73 | −40.9 ± 1.75 | 0.50 |
| **ApoB** | **n = 101** | **n = 104** | **n = 103** | |
| baseline mean | 147.3 | 144.6 | 146.5 | |
| final mean | 122.4 | 91.3 | 92.9 | |
| % change (mean ± SE) | −15.6 ± 1.53 | −36.3 ± 1.51 | −35.3 ± 1.52 | 0.62 |
| **ApoAI** | **n = 94** | **n = 97** | **n = 92** | |
| baseline mean | 141.3 | 140.6 | 142.2 | |
| final mean | 152.0 | 147.2 | 152.9 | |
| % change (mean ± SE) | 8.1 ± 1.81 | 6.2 ± 1.78 | 10.2 ± 1.83 | 0.12 |
| **hsCRP** | **n = 101** | **n = 104** | **n = 103** | |
| baseline median | 3.05 | 3.58 | 3.92 | |
| % change (median; Q1, Q3) | −12.1; −39.7, 28.4 | −33.8; −55.7, −5.2 | −39.3; −52.6, −9.0 | 0.55 |
| **VLDL-C** | **n = 99** | **n = 103** | **n = 100** | |
| baseline mean | 65.9 (1.71) | 69.6 (1.80) | 63.5 (1.64) | |
| final mean | 36.2 (0.94) | 38.6 (1.00) | 27.6 (0.71) | |
| % change (mean ± SE) | −37.2 ± 3.47 | −41.3 ± 3.40 | −52.0 ± 3.46 | 0.027 |
| **Total-C** | **n = 102** | **n = 106** | **n = 103** | |
| baseline mean | 260.0 (6.76) | 259.4 (6.74) | 259.4 (6.75) | |
| final mean | 224.7 (5.84) | 167.0 (4.34) | 172.7 (4.49) | |
| % change (mean ± SE) | −12.6 ± 1.34 | −35.3 ± 1.32 | −32.6 ± 1.33 | 0.14 |

a Means are presented in mg/dL (mmol/L); hsCRP medians are presented in mg/L.

b Fenofibric acid + moderate-dose statin compared with moderate-dose statin monotherapy.

**ApoAI** = apolipoprotein AI; **ApoB** = apolipoprotein B; **hsCRP** = high-sensitivity C-reactive protein; **non-HDL-C** = non-high-density lipoprotein cholesterol; **Q1** = first quartile; **Q3** = third quartile; **SE** = standard error; **total-C** = total cholesterol; **VLDL-C** = very low-density lipoprotein cholesterol.

compared with statin monotherapy. This may be interpreted by some clinicians to favor statin monotherapy. Recent trials suggest that the degree of LDL-C reduction with fibrate combination therapies is inversely related to baseline TG levels,[20,21] and directly related to higher baseline LDL-C levels,[11-13] which is consistent with the baseline lipids in our population. In support of these trial findings, the LDL-C reduction was similar between both statin doses of combination therapy and the corresponding statin monotherapy in the subgroup with high baseline LDL-C levels (>160 mg/dL). To further support this, reductions in ApoB and non-HDL-C, which more accurately reflect the atherogenic particle number, especially in patients with high triglycerides, were either greater or equivalent with combination therapy compared with statin monotherapy.

Our results demonstrate the significant increase in HDL-C with fenofibric acid monotherapy and combination therapy, resulting in final means near 44 mg/dL (1.14 mmol/L), as well as approximately 10% increases in ApoAI levels. The effects on HDL-C and ApoAI with fenofibric acid were strikingly different from those observed with fenofibrate treatment in the FIELD trial in patients with type 2 diabetes, in which no durable benefit on HDL-C or ApoAI levels was demonstrated.[22,23] This difference could be due to the higher baseline TG and lower HDL-C levels in our population compared with those in the FIELD trial. Important to the clinician, the substantial HDL-C increase was consistent among the three statin combination therapies (fenofibric acid + rosuvastatin, simvastatin or atorvastatin), and approximately twice the number of patients on combination therapy reached final

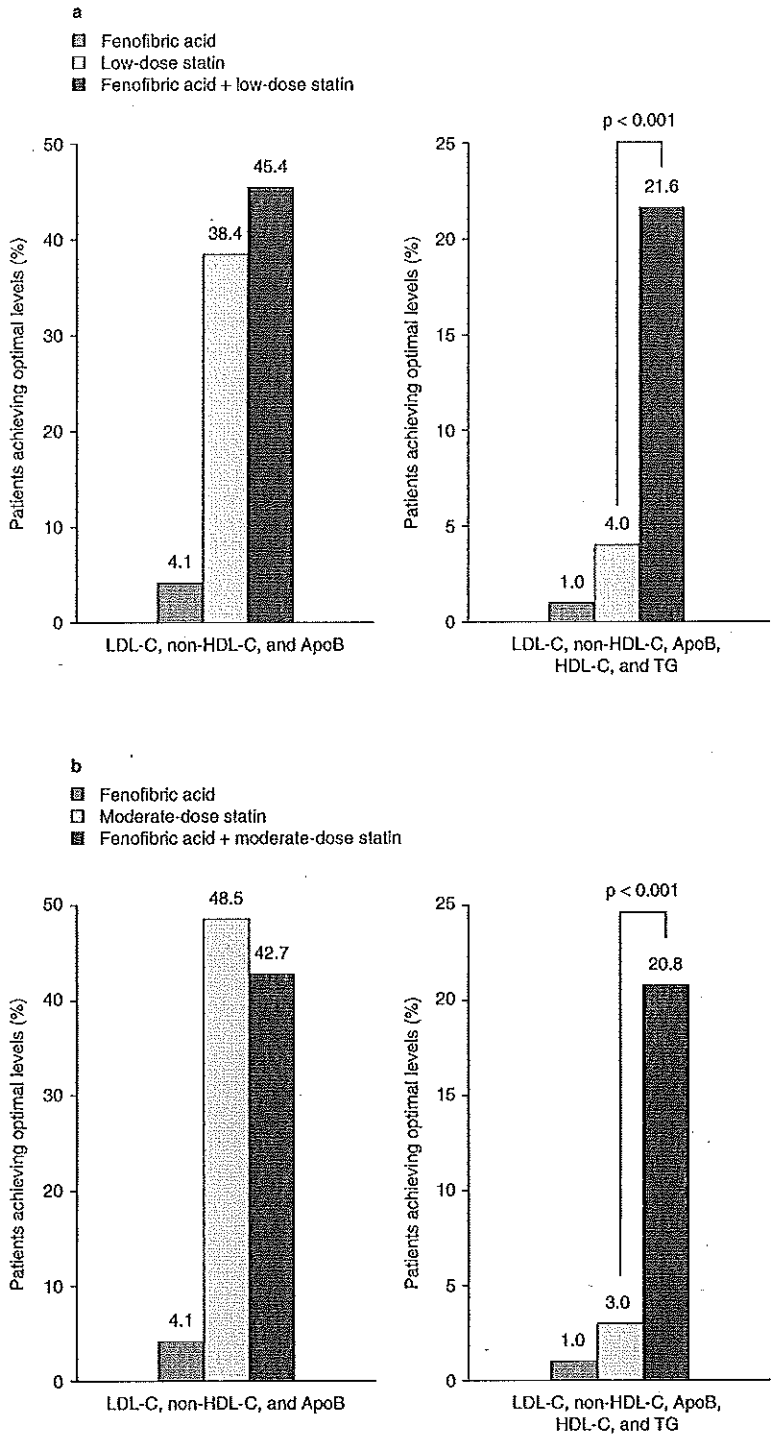


**Fig. 3.** Optimal lipid level achievement following treatment. The percentages of patients who simultaneously achieved low-density lipoprotein cholesterol (LDL-C) <100 mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) <130 mg/dL, and apolipoprotein B (ApoB) <90 mg/dL (left panels) at final visit; as well as the percentages of patients who simultaneously achieved LDL-C <100 mg/dL, non-HDL-C <130 mg/dL, ApoB <90 mg/dL, HDL-C >40 mg/dL (men)/>50 mg/dL (women), and triglycerides (TG) <150 mg/dL (right panels) at final visit are shown for (a) fenofibric acid 135 mg monotherapy, low-dose statin monotherapy, and fenofibric acid + low-dose statin combination therapy groups and (b) fenofibric acid 135 mg monotherapy, moderate-dose statin monotherapy, and fenofibric acid + moderate-dose statin combination therapy groups. p-Values are shown for statistically significant differences, comparing combination therapy with the corresponding dose of statin monotherapy.

Table IV. Summary of safety[a]

| Safety variable | Fenofibric acid | Low-dose statin | Fenofibric acid + low-dose statin | Moderate-dose statin | Fenofibric acid + moderate-dose statin |
|---|---|---|---|---|---|
| **Investigator-reported AEs** | | | | | |
| No. of subjects | 105 | 105 | 106 | 107 | 110 |
| Any treatment-emergent AE | 70 (66.7) | 57 (54.3) | 82 (77.4) | 72 (67.3) | 83 (75.5) |
| Myalgia | 1 (1.0) | 6 (5.7) | 2 (1.9) | 2 (1.9) | 3 (2.7) |
| Rhabdomyolysis | 0 | 0 | 0 | 0 | 0 |
| **Laboratory evaluations** | | | | | |
| No. of subjects | 103 | 102 | 104 | 106 | 107 |
| ALT >3×ULN on two consecutive visits | 2 (1.9) | 0 | 2 (1.9) | 0 | 1 (0.9) |
| AST >3×ULN on two consecutive visits | 0 | 0 | 0 | 0 | 0 |
| CK >5×ULN | 0 | 0 | 1 (1.0)[b] | 0 | 0 |
| CK >10×ULN | 0 | 0 | 1 (1.0)[b] | 0 | 0 |
| Creatinine >1.5×baseline and above ULN | 6 (5.8) | 2 (2.0) | 4 (3.8) | 0 | 4 (3.7) |
| Creatinine >2×baseline | 0 | 0 | 1 (1.0) | 0 | 0 |
| Mean change[c] in fasting blood glucose [mg/dL (mmol/L)] | −3.39 (−0.19) | + 12.87 (+0.71) | +2.88 (+0.16) | +9.59 (+0.53) | −0.15 (−0.01) |

a Data have been presented as n (%), except for mean change in fasting blood glucose.

b No. of subjects = 105.

c From baseline to final value.

**AEs** = adverse events; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **CK** = creatine kinase; **ULN** = upper limit of normal.

HDL-C levels of >40 (men) or >50 mg/dL (women), compared with statin monotherapy (data not shown).

In general, safety results in the subgroup of patients with type 2 diabetes were consistent with the results in the overall population, and suggest that combination therapy was generally well tolerated.[16] Specifically, there were no cases of rhabdomyolysis or new or unexpected safety concerns with combination therapy over 12 weeks. Although the duration of exposure to treatment was relatively short in this analysis, long-term (52-week) safety of fenofibric acid + moderate-dose statin combination therapy has been demonstrated in an open-label extension of these patients with mixed dyslipidemia, of which ~20% had type 2 diabetes.[15]

An intriguing observation was noted in mean changes in fasting blood glucose levels from baseline to final value, which were approximately 10 mg/dL (0.56 mmol/L) lower in the combination therapy groups than in the statin monotherapy groups. This result was unlikely to be due to differences in glucose treatment, as concomitant use of antidiabetes medication was similar among the groups. The clinical relevance of this observation is limited due to the lack of glycosylated hemoglobin ($HbA_{1c}$) measurements during the treatment phase and the relatively short duration of therapy (12 weeks). However, patients were required to have $HbA_{1c} \leq 8.5\%$ at trial enrollment and were on stable diabetes medication during the trial. Recent trials have suggested that statin treatment may slightly increase the risk of developing diabetes,[24,25] although this has not been a consistent finding.[26] Mechanistically, high-dose statin treatment has been shown to have no direct effect on insulin sensitivity or on intramuscular lipid content.[27,28] In contrast, some trials have demonstrated that fibrates have beneficial effects on insulin resistance,[29,30] although a recent trial using gold-standard techniques did not observe an effect of fenofibrate on insulin sensitivity in patients with the metabolic syndrome.[31] Taken together, these results would suggest that the effect of fenofibric acid as monotherapy and in combination with a statin on glucose metabolism warrants further evaluation.

Limitations of this analysis, in addition to those already mentioned, include the relatively large proportion of White patients, which hinders the generalization of these results to all racial populations. Given the relatively short duration of the primary trials included in this analysis, it was not possible to meaningfully evaluate clinical outcomes. High-dose statin monotherapy was not compared in this analysis, but is a treatment option for some patients with type 2 diabetes.

## Conclusions

The results of the current analysis demonstrate that treatment with fenofibric acid + statin combination therapy in patients with mixed dyslipidemia and type 2 diabetes was well tolerated and resulted in more comprehensive improvement to the abnormal lipid/apolipoprotein profile than either monotherapy.

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# Year Two Assessment of Fenofibric Acid and Moderate-Dose Statin Combination

## A Phase 3, Open-Label, Extension Study

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## Abstract

**Background and Objectives:** Long-term (>1 year) safety and efficacy studies of combination lipid therapy are lacking. This year 2 study evaluated fenofibric acid 135 mg in combination with moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg or atorvastatin 40 mg) in patients with mixed dyslipidaemia.

**Methods:** This was a phase 3, open-label, year 2 extension study in patients who had completed one of three double-blind, 12-week, controlled studies and the subsequent open-label, year 1 extension study. Patients in this study had mixed dyslipidaemia (high-density lipoprotein cholesterol [HDL-C] <40 mg/dL [<1.02 mmol/L] for men or <50 mg/dL [<1.28 mmol/L] for women, triglycerides [TG] ≥150 mg/dL [≥1.69 mmol/L], and low-density lipoprotein cholesterol [LDL-C] ≥130 mg/dL [≥3.37 mmol/L]) at the start of the controlled study, and had completed the year 1 extension study. Treatment was once-daily oral coadministration of fenofibric acid 135 mg and moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg or atorvastatin 40 mg), and was identical to the treatment received in the year 1 study. The year 2 population safety data were summarized for the entire duration of fenofibric acid + statin therapy. Efficacy data were summarized by combination therapy group, as well as pooled across combination therapies, and summarized across the controlled and open-label studies.

**Results:** Of the 310 patients enrolled into the year 2 study, 287 (93%) completed therapy. The mean cumulative exposure to combination therapy was 743 days across the studies. Adverse event rates were similar for all three combination therapy groups. No deaths or treatment-related serious adverse events occurred. The incidence of discontinuation due to adverse events was 2.9% overall. Rhabdomyolysis was not reported in any group. Overall, fenofibric acid + moderate-dose statin for ≥2 years resulted in sustained improvements in HDL-C (+17.4%), TG (–46.4%) and LDL-C (–40.4%).

**Conclusions:** This long-term study demonstrated that fenofibric acid + moderate-dose statin was generally well tolerated with no new or unexpected safety concerns, and resulted in comprehensive and sustained lipid improvements in patients with mixed dyslipidaemia.
Registered at clinicaltrials.gov: NCT00491530.

## Background

Abnormal blood concentrations of lipids and lipoproteins such as low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) are associated with increased risk for coronary heart disease (CHD),[1-4] the leading cause of death in the US.[5] Recommended lipid therapies to reduce CHD risk have focused on lifestyle changes and LDL-C-lowering statin monotherapy. However, treatment with a statin is often insufficient to significantly improve or normalize multiple CHD lipid risk factors. The presence of mixed dyslipidaemia, a common lipid disorder characterized by elevated LDL-C, low HDL-C and high TG levels, is associated with significantly greater risk for cardiovascular events compared with isolated elevated LDL-C.[6] Therefore, substantial residual risk of cardiovascular events may exist in statin-treated patients when high TG and low HDL-C remain inadequately treated.[7] The combination of a statin with another lipid-modifying drug that targets these additional lipid abnormalities may be a more appropriate therapy in these patients.

The co-administration of a statin and a fibrate (fibric acid derivative) has been demonstrated to be an effective therapy for simultaneously improving multiple lipid abnormalities, resulting in incremental improvements over monotherapy.[8-14] The use of a statin/fibrate combination is becoming more common in clinical practice; however, the available clinical data regarding this treatment option are primarily from relatively short-term studies. In particular, the long-term (>1 year) safety of combination therapy has not been adequately addressed in the available clinical trial literature. The US FDA has approved an indication for the use of fenofibric acid choline salt in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidaemia and CHD or a CHD-risk equivalent who are on optimal statin therapy to achieve their LDL-C goal. Reported here are the results of the safety and efficacy analyses of patients with mixed dyslipidaemia who were treated with open-label fenofibric acid 135 mg + moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg or atorvastatin 40 mg) for at least 2 years.

## Patients and Methods

### Clinical Programme

The fenofibric acid clinical development programme consisted of three similarly designed, 12-week, multicentre, phase 3, double-blind, randomized, controlled studies and two subsequent, 52-week, phase 3, open-label, extension studies (figure 1).[15] The three controlled studies evaluated fenofibric acid (Trilipix®, Abbott, North Chicago, IL, USA) + statin combination therapies and individual monotherapies. Each study used a separate statin (rosuvastatin [CRESTOR®, AstraZeneca, Wilmington, DE, USA],[12] simvastatin [ZOCOR®, Merck, Whitehouse Station, NJ, USA][13] or atorvastatin [LIPITOR®, Pfizer, New York, NY, USA][10]). The treatment dose groups were: fenofibric acid 135 mg, low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg or atorvastatin 20 mg), moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg or atorvastatin 40 mg), high-dose statin (rosuvastatin 40 mg, simvastatin 80 mg or atorvastatin 80 mg), fenofibric acid + low-dose statin, or fenofibric acid + moderate-dose statin. The first 52-week, open-label extension study (referred to as year 1) evaluated fenofibric acid + moderate-dose statin.[16] Patients received fenofibric acid and the same statin (rosuvastatin,

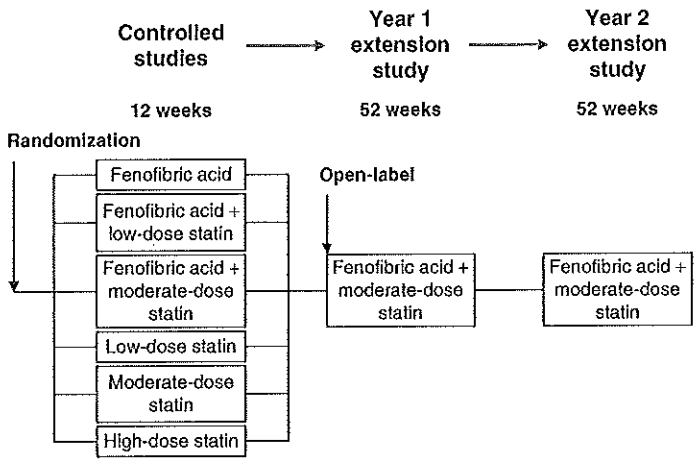


**Fig. 1.** Study design. The duration and treatment groups of the clinical programme phase 3 studies are shown. In the controlled studies, patients were randomized in a 2:2:2:2:2:1 ratio to fenofibric acid 135 mg, fenofibric acid + low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg or atorvastatin 20 mg), fenofibric acid + moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg or atorvastatin 40 mg), low-dose statin, moderate-dose statin or high-dose statin (rosuvastatin 40 mg, simvastatin 80 mg or atorvastatin 80 mg). Patients who completed a controlled study (regardless of treatment received) were eligible to enrol in the open-label year 1 study. A subset of sites was selected to enrol patients in the open-label year 2 study. Only patients who enrolled in the year 2 extension study were included in this analysis.

simvastatin or atorvastatin) used in the statin-containing arms of the controlled study in which they participated. Patients received the identical combination therapy in the second 52-week, open-label extension study (NCT00491530; referred to as year 2) as they received in the year 1 study. Visits in the year 2 study were conducted between 28 June 2007 and 2 November 2008 and occurred at baseline and at weeks 8, 16, 28, 40 and 52.

### Patients

Patients were eligible to enrol in one of the three controlled studies if they were aged ≥18 years, non-pregnant and had mixed dyslipidaemia (HDL-C <40 mg/dL [<1.02 mmol/L] for men or <50 mg/dL [<1.28 mmol/L] for women, TG ≥150 mg/dL [≥1.69 mmol/L] and LDL-C ≥130 mg/dL [≥3.37 mmol/L]) after a 6-week period of diet[17] run-in and washout of lipid-altering medications. Patients with type 1 diabetes mellitus, uncontrolled type 2 diabetes (glycosylated haemoglobin [$HbA_{1c}$] >8.5%) or unstable cardiovascular disease were excluded. A study size ratio of approximately 2:1:1 was planned for the controlled studies evaluating fenofibric acid + rosuvastatin, simvastatin or atorvastatin, respectively.

Patients who completed the controlled studies at all participating sites (regardless of treatment received) were eligible to enrol into the year 1 study, and a subset of sites from the year 1 study was selected to enrol patients in the year 2 study. The planned year 2 study size of approximately 300 patients (150 receiving fenofibric acid + rosuvastatin and 75 subjects each receiving fenofibric acid + simvastatin and fenofibric acid + atorvastatin) was determined with consideration to obtaining sufficient safety information during exposure to combination therapy, and reflected the 2:1:1 ratio of patients participating in the controlled studies. Sites were selected to participate in the year 2 study based on investigator interest, geography (only US sites were included), and demonstrated site performance in the preceding studies. Patients from year 2 participating sites were eligible to enrol if they had completed the year 1 study. Exclusion criteria included development of an exclusionary medical condition, or requirement for exclusionary medication.[15]

### Analyses

All patients who enrolled into the year 2 extension study were analysed. Safety was assessed by evaluating investigator-reported adverse

events (AEs), physical examination findings, changes in vital signs, and laboratory values. Safety data were summarized by combination therapy group and for all patients combined, for the entire duration of combination therapy (up to 116 weeks). Investigator-reported AEs with a start date on or after first dose of combination therapy through 30 days post-treatment were summarized. AEs assessed by the investigator as 'possibly related' or 'probably related' to study drug were deemed treatment-related AEs. Laboratory measurements related to muscle, renal or hepatic function were also evaluated during combination therapy and baseline was defined as the treatment-naïve baseline value in the controlled studies at the time of randomization.

Efficacy data were summarized by combination therapy group, as well as pooled across the different statins utilized in the study and summarized as a single group. For efficacy analyses, baseline was also defined as the treatment-naïve baseline value in the controlled studies at the time

**Table I.** Year 2 study patient demographics and baseline characteristics[a]

| Demographic/characteristic | Fenofibric acid 135 mg + rosuvastatin 20 mg (n = 174) | Fenofibric acid 135 mg + simvastatin 40 mg (n = 50) | Fenofibric acid 135 mg + atorvastatin 40 mg (n = 86) | Total (n = 310) |
|---|---|---|---|---|
| Sex [n (%)] | | | | |
| women | 77 (44.3) | 29 (58.0) | 42 (48.8) | 148 (47.7) |
| men | 97 (55.7) | 21 (42.0) | 44 (51.2) | 162 (52.3) |
| Race [n (%)] | | | | |
| White | 164 (94.3) | 49 (98.0) | 80 (93.0) | 293 (94.5) |
| Black | 6 (3.4) | 1 (2.0) | 2 (2.3) | 9 (2.9) |
| other | 0 (0.0) | 0 (0.0) | 4 (4.7) | 4 (1.3) |
| multi-race | 4 (2.3) | 0 (0.0) | 0 (0.0) | 4 (1.3) |
| Ethnicity [n (%)][b] | | | | |
| Hispanic | 20 (11.5) | 1 (2.0) | 4 (4.7) | 25 (8.1) |
| Age (y) [mean (SD)] | 56.1 (10.71) | 55.3 (10.55) | 55.4 (10.94) | 55.8 (10.72) |
| Bodyweight (kg) [mean (SD)] | | | | |
| women | n = 77<br>87.5 (20.23) | n = 29<br>81.5 (17.01) | n = 42<br>84.1 (18.78) | n = 148<br>85.3 (19.26) |
| men | n = 97<br>99.8 (20.16) | n = 21<br>97.7 (16.17) | n = 44<br>99.6 (14.45) | n = 162<br>99.5 (18.20) |
| Waist circumference (cm) [mean (SD)] | | | | |
| women | n = 76<br>101.1 (14.09) | n = 29<br>95.2 (12.40) | n = 42<br>100.3 (15.24) | n = 147<br>99.7 (14.20) |
| men | n = 97<br>106.0 (13.99) | n = 21<br>105.6 (11.32) | n = 43<br>106.9 (12.64) | n = 161<br>106.2 (13.25) |
| Tobacco use [n (%)] | | | | |
| user | 33 (19.0) | 12 (24.0) | 15 (17.4) | 60 (19.4) |
| ex-user | 51 (29.3) | 16 (32.0) | 22 (25.6) | 89 (28.7) |
| non-user | 90 (51.7) | 22 (44.0) | 49 (57.0) | 161 (51.9) |
| Co-morbidities [n (%)] | | | | |
| coronary artery disease[c] | 12 (6.9) | 3 (6.0) | 6 (7.0) | 21 (6.8) |
| hypertension[c] | 92 (52.9) | 29 (58.0) | 49 (57.0) | 170 (54.8) |
| type 2 diabetes mellitus[c] | 44 (25.3) | 19 (38.0) | 19 (22.1) | 82 (26.5) |

a Data were collected at the start of the controlled studies.

b Statistically significant differences in the percentage of patients reporting Hispanic ethnicity were observed among treatment groups ($p = 0.037$, chi-squared [$\chi^2$] test).

c Reported medical history.

**Table II.** Incidence of investigator-reported adverse events (AEs) during combination therapy[a,b]

| AEs | Fenofibric acid 135 mg + rosuvastatin 20 mg (n = 174) | Fenofibric acid 135 mg + simvastatin 40 mg (n = 50) | Fenofibric acid 135 mg + atorvastatin 40 mg (n = 86) | Total (n = 310) |
|---|---|---|---|---|
| Deaths | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| SAEs[c] | 26 (14.9) | 4 (8.0) | 5 (5.8) | 35 (11.3) |
| Treatment-related SAEs | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| AEs leading to discontinuation | 6 (3.4) | 1 (2.0) | 2 (2.3) | 9 (2.9) |
| Treatment-related AEs | 49 (28.2) | 19 (38.0) | 26 (30.2) | 94 (30.3) |

a AEs with a start date on or after the first dose of combination therapy, either in the controlled studies or the year 1 open-label study, through 30 days after the last dose of combination therapy in the year 2 study are summarized. No statistically significant difference in incidence was observed among treatment groups.

b Data are given as n (%).

c The definition of an SAE was based on the criteria of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines.

**SAE** = serious AE.

of randomization, following the 6-week washout period. Efficacy variables were mean percentage changes from baseline in HDL-C, TG, LDL-C, non-HDL-C, total cholesterol (total-C) and very LDL-C (VLDL-C). Data were analysed as observed. Efficacy data for the subgroup of patients with type 2 diabetes, as reported in their medical history, were also analysed.

All statistical comparisons were performed *post hoc*. Baseline characteristics and safety analyses were compared among treatment groups using a chi-squared ($\chi^2$) test for categorical variables and a one-way ANOVA for continuous variables. For efficacy analyses, baseline and week 116 values were compared within each treatment group using a paired t-test. Mean percentage changes in efficacy variables were compared among treatment groups using a one-way ANOVA.

## Results

### Patient Disposition and Duration of Therapy

A total of 310 patients were enrolled and treated in this year 2 extension study; 174 received fenofibric acid 135 mg + rosuvastatin 20 mg (fenofibric acid + rosuvastatin), 50 received fenofibric acid + simvastatin 40 mg (fenofibric acid + simvastatin), and 86 received fenofibric acid + atorvastatin 40 mg (fenofibric acid + atorvastatin). A total of 287 (92.6%) patients completed the study: 162 in the fenofibric acid + rosuvastatin group, 44 in the fenofibric acid + simvastatin group, and 81 in the fenofibric acid + atorvastatin group. Patient characteristics are shown in table I. The mean duration of cumulative exposure to combination therapy was 743 days across the studies, and was similar among all three combination therapy groups. The duration of exposure ranged from 376 to 841 days in the fenofibric acid + rosuvastatin group, 488 to 839 days in the fenofibric acid + simvastatin group, and 366 to 846 days in the fenofibric acid + atorvastatin group.

### Safety

No death occurred during this year 2 study. The incidence of investigator-reported serious AEs during exposure to combination therapy across the studies was numerically highest in the fenofibric acid + rosuvastatin group (14.9%) compared with the fenofibric acid + simvastatin (8.0%) or fenofibric acid + atorvastatin (5.8%) groups; however, no significant differences were observed among treatment groups and no serious AE was considered by the investigator to be treatment-related (table II). The incidence of AEs throughout the entire duration of combination therapy was also similar among all three combination therapy groups (94.8% [fenofibric acid + rosuvastatin], 90.0% [fenofibric acid + simvastatin], and 97.7% [fenofibric acid + atorvastatin]). AEs tended to occur early in treatment, without the emergence of new types of AEs over time (table III).

**Table III.** Incidence of first occurrence of adverse events (AEs) over time

| Treatment group | Exposure interval at onset of AE [n (%)][a] | | | | |
|---|---|---|---|---|---|
| | 1–12 | 13–26 | 27–40 | 41–54 | 55–68 |
| **Weeks** | | | | | |
| Fenofibric acid 135 mg + rosuvastatin 20 mg | n = 174<br>103 (59.2) | n = 174<br>36 (50.7) | n = 174<br>14 (40.0) | n = 174<br>3 (14.3) | n = 174<br>3 (16.7) |
| Fenofibric acid 135 mg + simvastatin 40 mg | n = 50<br>37 (74.0) | n = 50<br>6 (46.2) | n = 50<br>0 (0.0) | n = 50<br>1 (14.3) | n = 50<br>0 (0.0) |
| Fenofibric acid 135 mg + atorvastatin 40 mg | n = 86<br>53 (61.6) | n = 86<br>18 (54.5) | n = 86<br>4 (26.7) | n = 86<br>5 (45.5) | n = 86<br>0 (0.0) |
| **Weeks** | **69–82** | **83–96** | **97–110[b]** | **111–124[b]** | **Total** |
| Fenofibric acid 135 mg + rosuvastatin 20 mg | n = 168<br>3 (20.0) | n = 168<br>2 (16.7) | n = 164<br>1 (10.0) | n = 58<br>0 (0.0) | n = 174<br>165 (94.8) |
| Fenofibric acid 135 mg + simvastatin 40 mg | n = 50<br>1 (16.7) | n = 48<br>0 (0.0) | n = 46<br>0 (0.0) | n = 20<br>0 (0.0) | n = 50<br>45 (90.0) |
| Fenofibric acid 135 mg + atorvastatin 40 mg | n = 84<br>2 (33.3) | n = 84<br>2 (50.0) | n = 82<br>0 (0.0) | n = 29<br>0 (0.0) | n = 86<br>84 (97.7) |

a Percentages were calculated as follows: for each time period, the numerator was the number of patients who had the first occurrence of an AE with onset in that time period and the denominator was all patients who took combination therapy during the time period or within 30 days prior to the beginning of the time period (n) and did not have an AE with an onset date within a previous period.

b Only patients who were randomized to combination therapy in the controlled studies could have been treated for >104 weeks.

The incidence of treatment-related AEs during combination therapy was similar among treatment groups. The most common treatment-related AEs were muscle spasms (3.9%), increased blood creatine phosphokinase (CPK) [3.5%], headache (2.9%), myalgia (2.9%), dyspepsia (2.3%) and nausea (2.3%). Rhabdomyolysis was not reported in any group. A total of nine patients discontinued therapy in the year 2 study due to AEs, with similar incidences among combination therapy groups (table II). Myalgia leading to discontinuation was reported by two patients

**Table IV.** Incidence of elevations in laboratory values related to hepatic, muscle and renal function during combination therapy[a,b]

| Function | Fenofibric acid 135 mg + rosuvastatin 20 mg (n = 174) | Fenofibric acid 135 mg + simvastatin 40 mg (n = 50) | Fenofibric acid 135 mg + atorvastatin 40 mg (n = 86) | Total (n = 310) |
|---|---|---|---|---|
| **Hepatic** | | | | |
| ALT >3 × ULN on 2 consecutive visits | 2 (1.1) | 0 (0.0) | 0 (0.0) | 2 (0.6) |
| AST >3 × ULN on 2 consecutive visits | 1 (0.6) | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Discontinued with ALT and/or AST >3 × ULN on 2 consecutive visits | 1 (0.6) | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| **Muscle** | | | | |
| CPK >10 × ULN | 3 (1.7) | 0 (0.0) | 1 (1.2) | 4 (1.3) |
| CPK >5 × ULN | 4 (2.3) | 0 (0.0) | 1 (1.2) | 5 (1.6) |
| Discontinued with CPK >5 × ULN | 1 (0.6) | 0 (0.0) | 1 (1.2) | 2 (0.6) |
| **Renal** | | | | |
| Creatinine >2 mg/dL (>176.8 μmol/L) | 3 (1.7) | 2 (4.0) | 1 (1.2) | 6 (1.9) |
| Creatinine ≥2 × baseline[c] | 3 (1.7) | 3 (6.0) | 1 (1.2) | 7 (2.3) |
| Discontinued with creatinine ≥2 × baseline | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

a Data are given as n (%).

b No statistically significant difference in incidence was observed among treatment groups.

c Baseline for safety analyses was the treatment-naïve baseline value in the controlled studies at the time of randomization following the 6-week washout period.

**ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **CPK** = creatine phosphokinase; **ULN** = upper limit of normal.

**Table V.** Mean values[a] and percentage changes from baseline to week 116 in lipid efficacy variables

| Variable | Fenofibric acid 135 mg + rosuvastatin 20 mg (n = 174) | Fenofibric acid 135 mg + simvastatin 40 mg (n = 50) | Fenofibric acid 135 mg + atorvastatin 40 mg (n = 86) | p-Value[b] |
|---|---|---|---|---|
| **HDL-C** | | | | |
| n | 161 | 41 | 79 | |
| Baseline[c] | 38.3 (0.99) | 39.5 (1.02) | 38.0 (0.99) | |
| Week 116 | 45.0 (1.17) | 46.5 (1.20) | 42.4 (1.10) | |
| % change ± SD | +19.2 ± 25.23 | +18.6 ± 20.48 | +13.1 ± 22.91 | 0.17 |
| **TG** | | | | |
| n | 161 | 41 | 79 | |
| Baseline[c] | 294.5 (3.33) | 239.0 (2.70) | 286.0 (3.23) | |
| Week 116 | 137.5 (1.55) | 127.4 (1.44) | 129.9 (1.47) | |
| % change ± SD | −48.2 ± 22.61 | −41.8 ± 24.72 | −45.0 ± 39.45 | 0.40 |
| **LDL-C** | | | | |
| n | 159 | 41 | 79 | |
| Baseline[c] | 152.5 (3.95) | 159.4 (4.13) | 158.6 (4.11) | |
| Week 116 | 87.0 (2.25) | 96.7 (2.50) | 89.2 (2.31) | |
| % change ± SD | −40.9 ± 20.66 | −37.8 ± 14.21 | −40.8 ± 19.20 | 0.66 |
| **Non-HDL-C** | | | | |
| n | 161 | 41 | 79 | |
| Baseline[c] | 222.6 (5.77) | 216.2 (5.60) | 219.9 (5.70) | |
| Week 116 | 113.2 (2.93) | 123.9 (3.21) | 113.6 (2.94) | |
| % change ± SD | −48.6 ± 13.58 | −41.7 ± 13.10 | −47.3 ± 12.50 | 0.011 |
| **Total-C** | | | | |
| n | 161 | 41 | 79 | |
| Baseline[c] | 260.9 (6.78) | 255.8 (6.65) | 257.9 (6.71) | |
| Week 116 | 158.1 (4.11) | 170.3 (4.43) | 156.0 (4.06) | |
| % change ± SD | −38.7 ± 12.16 | −32.5 ± 10.86 | −38.6 ± 10.85 | 0.007 |
| **VLDL-C** | | | | |
| n | 152 | 39 | 79 | |
| Baseline[c] | 71.4 (1.85) | 58.0 (1.50) | 61.3 (1.59) | |
| Week 116 | 26.6 (0.69) | 27.4 (0.71) | 24.4 (0.63) | |
| % change ± SD | −56.8 ± 25.17 | −40.3 ± 51.25 | −51.2 ± 35.42 | 0.019 |

a Presented as mg/dL (mmol/L).

b Mean percentage changes were compared among treatment groups using one-way ANOVA with effect for treatment group.

c Baseline was defined as the treatment-naïve baseline value in the controlled studies at the time of randomization, following the 6-week washout period.

**HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **SD** = standard deviation; **TG** = triglyceride; **total-C** = total cholesterol; **VLDL-C** = very low-density lipoprotein cholesterol.

(both receiving fenofibric acid + rosuvastatin); all other AEs leading to discontinuation were reported by only one patient each.

Laboratory elevations that occurred during combination therapy and met predefined criteria for clinically relevant hepatic, muscle and renal-related laboratory abnormalities are shown in table IV for the year 2 population. No statistically significant difference in the incidence of these laboratory elevations was observed among treatment groups (table IV). Of the patients with increases in ALT and/or AST to >3 × the upper limit of normal (ULN) on two consecutive visits, none had a concomitant increase in bilirubin to

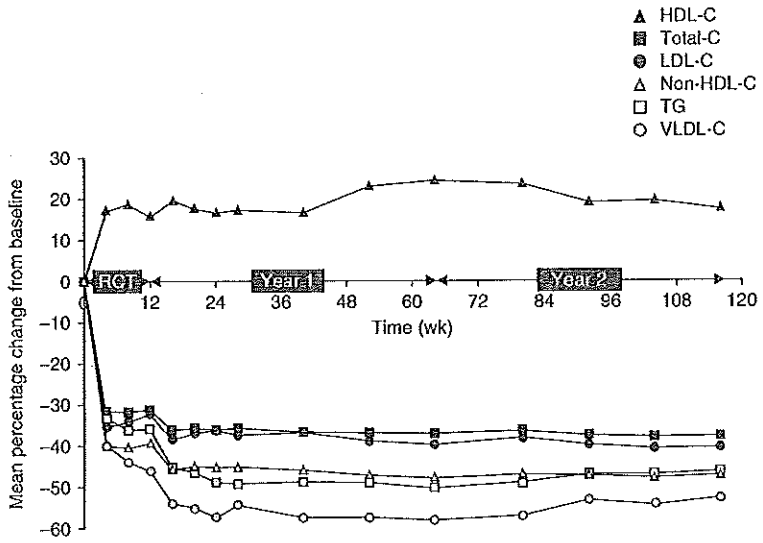


**Fig. 2.** Long-term efficacy. Mean percentage change from baseline to each visit is shown for each variable. Data were pooled and summarized as one group. The three controlled studies (randomized controlled trials [RCTs]) lasted for 12 weeks, and the two subsequent open-label extension studies (year 1 and year 2) lasted for 52 weeks each. **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **TG** = triglycerides; **total-C** = total cholesterol; **VLDL-C** = very LDL-C.

>2×ULN. Four patients had elevations in CPK >10×ULN and one patient with CPK >10×ULN in the fenofibric acid + rosuvastatin group reported concomitant myalgia. This was a single episode that lasted 12 days, was considered mild in severity, and was determined by the investigator to be not related to treatment. The myalgia did not result in premature discontinuation, and CPK levels resolved within 9 days. One patient in the fenofibric acid + rosuvastatin group discontinued with creatinine ≥1.5×the baseline value.

Premature discontinuations with laboratory elevations that met predefined criteria for clinically relevant abnormalities were rare (table IV). In the overall population, minor mean increases from the treatment-naïve baseline to final value in year 2 in ALT, AST, CPK and creatinine levels were observed, and minor mean decreases from baseline to final value in year 2 in alkaline phosphatase were observed.

## Efficacy

At baseline (i.e. at randomization into the controlled studies), the overall mean levels of lipid parameters were: HDL-C 38.5 mg/dL (1.00 mmol/L), TG 281.0 mg/dL (3.18 mmol/L), LDL-C 155.1 mg/dL (4.02 mmol/L), non-HDL-C 220.9 mg/dL (5.72 mmol/L), total-C 259.4 mg/dL (6.74 mmol/L), and VLDL-C 66.3 mg/dL (1.72 mmol/L). These baseline levels were reflective of untreated patients with mixed dyslipidaemia. Efficacy data were summarized for each combination therapy group (table V) as well as pooled and summarized as one group (figure 2). Data in figure 2 demonstrate that the overall mean percentage changes in all efficacy variables were relatively large in the 12-week, double-blind controlled studies. Incremental improvements in mean percentage changes in all efficacy variables were observed after the first visit in the year 1 extension study (week 16), when all patients were taking open-label fenofibric acid + moderate-dose statin. This effect was sustained for ≥2 years and sizable mean percentage changes in all efficacy variables were observed at week 116 (table V and figure 2). In the overall population, the mean percentage changes from baseline to week 116 in efficacy variables were: +17.4% (HDL-C), −46.4% (TG), −40.4% (LDL-C), −47.3% (non-HDL-C), −37.8% (total-C) and −52.8% (VLDL-C). Statistically significant differences among treatment

groups in mean percentage changes were observed for non-HDL-C, total-C and VLDL-C (table V). For all three of these variables, the mean percentage changes were smaller in the fenofibric acid + simvastatin group.

In the subgroup of patients with type 2 diabetes, large mean percentage changes in HDL-C (+15.0%), TG (−42.1%), LDL-C (−41.8%), non-HDL-C (−48.2%), total-C (−39.4%) and VLDL-C (−54.6%) were observed from baseline to week 116 (n = 74 for each). These improvements were similar to those observed in the overall population.

## Discussion

The use of statin and fibrate combination therapy is becoming more common in clinical practice for patients with multiple CHD lipid risk factors, yet clinical trial data to evaluate the long-term safety and efficacy of this combination have been limited. Previous studies of 12-week or 1-year exposure to fenofibric acid + statin combination therapy demonstrated that this combination was generally well tolerated in patients with mixed dyslipidaemia, and no new or unexpected safety concerns were observed beyond those associated with each monotherapy.[10,12,13,16] The current results with 2-year exposure to fenofibric acid + statin combination therapy are consistent with these observations. Baseline characteristics of the year 2 population were similar to those described in the controlled studies and the year 1 study, suggesting that the year 2 population was a representative subset of the larger cohort previously evaluated (n = 2201, year 1 population), with respect to demographics and co-morbidities.

The overall incidence of premature discontinuation from the year 2 study was low (7.4%). Similarly, the incidence of discontinuation due to an AE was lower in the treated year 2 population (2.9% overall) compared with the treated year 1 population (9.3% overall). These results are consistent with the finding that the majority of AEs first occurred early in treatment exposure, and further demonstrate the long-term tolerability of fenofibric acid + statin combination therapy. Although the incidence of serious AEs in the year 2 population (11.3% overall) was higher than that reported in the year 1 study population (6.7% overall), none were reported by the investigator to be treatment related.

In spite of the clinical utility of combination therapy with a fibrate and a statin, the lack of long-term clinical data, especially related to muscle-related safety, has limited the clinician's ability to make evidence-based decisions about this treatment. These 2-year data confirm the known safety profile of the combination, as the incidence of myalgia and CPK elevations in the year 2 population were generally similar to those observed in the controlled studies and the year 1 study population. The incidence of creatinine ≥2 × baseline in the year 2 population (2.3% overall) was higher than that observed in the year 1 population (0.9% overall). However, no patient discontinued with creatinine ≥2 × baseline in the year 2 study and the incidence of creatinine >2 mg/dL in the year 2 population (1.9% overall) was comparable to that observed in the year 1 population (1.3% overall). The mean change in creatinine from the treatment-naïve baseline to final value in year 2 was 0.11 mg/dL (9.7 μmol/L) overall, with a range of 0.10 mg/dL (8.8 μmol/L; fenofibric acid + rosuvastatin) to 0.15 mg/dL (13.3 μmol/L; fenofibric acid + simvastatin). These changes in creatinine levels are consistent with findings in previous studies of fenofibric acid or fenofibrate.[16,18,19]

Previous analysis of the integrated controlled studies population demonstrated that fenofibric acid + low- or moderate-dose statin combination therapy resulted in significantly greater improvements in HDL-C and TG, compared with low- or moderate-dose statin monotherapy, respectively, and significantly greater decreases in LDL-C, compared with fenofibric acid monotherapy.[20] Since four of six treatment arms in the controlled studies were monotherapy, most patients in the current study transitioned to fenofibric acid + moderate-dose statin combination therapy in the year 1 study. This resulted in incremental improvements, seen initially at the first evaluation at 4 weeks into the year 1 study, in mean percentage changes of all efficacy variables. This effect was sustained for the duration of the year 1

and year 2 studies, and the year 2 values were consistent with those observed in the year 1 study population. The overall mean values of these lipid/lipoproteins after 2 years of fenofibric acid + moderate-dose statin therapy were all within optimal levels recommended by national guidelines.[3,21]

Over the course of open-label therapy with fenofibric acid + moderate-dose statin (from week 12 to week 116), some fluctuation was observed in the mean percentage changes in HDL-C and VLDL-C; however, the range was relatively small and the mean percentage changes at week 116 in HDL-C (+17.4%) and VLDL-C (−52.8%) were sizable and consistent with those observed in shorter-term trials of fenofibric acid + statin.[10,12,13] The improvements in efficacy variables in the subgroup of patients with type 2 diabetes were also sizable and consistent with those observed in the overall population. Notably, the increase in HDL-C over 2 years in the subgroup of patients with type 2 diabetes was higher than those increases observed with fenofibrate in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, in which little durable effect on HDL-C levels was observed.[19] These differences are at least partly due to the distinct patient populations evaluated, as well as to the differences in mean baseline HDL-C levels, which were higher in the FIELD study than in the current analysis.

The small proportion of non-White patients in this study limits the ability to generalize these results to other racial populations. Further studies that evaluate the effect of this combination therapy in different racial and ethnic populations are warranted. Other limitations of the study include the open-label design without a comparator or placebo arm, the lack of clinical outcomes assessment, and the fact that only a subset of sites that participated in the larger year 1 study were included in the year 2 study.

## Conclusion

These results provide relevant safety and efficacy data over 2 years and demonstrate that long-term treatment with fenofibric acid + moderate-dose statin combination therapy was generally well tolerated with no new or unexpected safety concerns, and resulted in comprehensive and sustained improvements in multiple lipid levels in patients with mixed dyslipidaemia.

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